REMARKS/ARGUMENTS

Claims 1-31 are pending, with claims 1, 3-14, 16 and 17 under consideration as a result of the restriction requirement of 5 March 2010 and the response of 5 April 2010. Claims 2, 15 and 18-31 are withdrawn. New dependent claim 32 is presented.

Priority and IDS

Applicant respectfully notes the acknowledgement of the priority documents and the review of the IDS that were filed on 17 August 2006 and 28 August 2009.

Claim amendments

Claim 1 is amended to include a specific quantity range for the NSAID present in the pharmaceutical preparation. This is effectively an incorporation of claim 4 (where support is found) into claim 1, so claim 4 is cancelled.

Claim 8 is amended to change occurrences of "optionally" to "present, if at all," and the occurrences of "optimal" amounts are removed. These optimal amounts are included in a new dependent claim 32 that depends from claim 8.

Claim 12 is amended to remove a "preferably."

No new matter is presented in making these amendments.

Section 112 rejections

All of the Examiner's claim rejections under 35 USC 112 are addressed in the claim amendments and are now believed to be mooted thereby.

Claim objections

The Examiner's objection to claim 17 is believed to be resolved by the amendment to claim 12 discussed above.

Section 103 rejections

Claims 1, 3-12, 14, 16 and 17 are rejected as obvious over WO 03/094905 to Pinza ("Pinza '905") and US 5,183,829 to Caldwell ("Caldwell '829"). The Applicant respectfully traverses.

Further, the identical set of claims is rejected as obvious over Pinza '905 and Caldwell '829 with the addition of US Pat 6,013,281 to Lundberg (Lundberg '281). Applicant also traverses this rejection.

Pinza '905 and Caldwell '829

As detailed above, applicant has amended the claims to clarify that the novel pharmaceutical preparation, *intended for local effect within the oral cavity in the form of an aqueous solution of flurbiprofen*, is in a concentration range of between 1.5 mg/ml and 8.0 mg/ml. This concentration range (flurbiprofen from 0.15% to 0.8 %) differs from Pinza's diclofenac itself and from diclofenac "net range" in diclofenac tromethamine (from 0.07% to 0.14%, as later on calculated). The claimed concentration is *not* suitable to yield any systemic effects in contrast to that of Caldwell '829. Therefore, it would still be clear to a skilled person that the solution of the current invention is only suitable for use in the oral cavity.

One of the aims of the current invention is to provide a medicinal product for self-medication with anti-inflammatory and analgesic properties for spraying into/onto the mouth, throat and gums which meets a number of ideal criteria, including the following:

(a) satisfactory anti-inflammatory and analgesic activity, both for reducing congestion and for alleviating the associated pain; the active ingredient must furthermore be homogeneously dissolved in the solution so that it can be sprayed uniformly into the oral cavity;

(b) the solution must be pharmaceutically stable and the active and auxiliary ingredients must accordingly not react with one another;

(c) the solution must be biologically acceptable to the oral mucosa, and thus neither excessively acidic, so as not to attack the dentine, nor excessively basic, so as not to exacerbate the irritation;

(d) provision of a mild disinfectant action to protect the mouth and pharynx from any bacterial and viral attack;

(e) have a preservative action to protect the solution from bacterial contamination and proliferation during production and subsequent use; and

(f) be organoleptically acceptable since it is intended for an organ which is particularly delicate and sensitive to unpleasant flavours and odour.

The solution as defined by the current invention advantageously possesses all of these criteria. No pharmaceutical composition exists which combines all of these

features. When considering the prior art documents either individually or in combination, a skilled person would never have arrived at the current invention without application of extensive experimentation and/or inventive skill.

In contrast to claim 1, Pinza '905 discloses a composition for the topical treatment of the oropharyngeal cavity disorders, comprising an aqueous solution of the salt of diclofenac with tromethamine, in which the amount of the said salt is of from 0.1% to 0.2% (w/w) and the pH is adjusted between 7 and 8. The technical problem actually addressed by Pinza '905 is the provision of a diclofenac-based composition having a pleasant, or at the least neutral taste, for the topical treatment of oropharyngeal cavity disorders (see page 2, lines 3 to 5 of Pinza), and which is completely different to that of the present invention.

In fact, by calculating the content of diclofenac (MW 296.15 = 70.09%) and tromethamine (MW 121.13 = 29.91%) in Pinza's diclofenac tromethamine salt (MW 417.28 = 100.0%) the "real net" range of diclofenac in the salt (as used in the range from 0.1% to 0.2% in WO03094905) would be in the range from 0.07% to 0.14%, and therefore below the flurbiprofen range (from 0.15% to 0.8%) of the instant invention.

Therefore, Pinza '905 discloses buccal sprays comprising both diclofenac and tromethamine as a salt. In contrast, the scope of the current invention relates to a solution containing flurbiprofen only and even then in a different higher concentration range. Hence, there is no disclosure in Pinza of providing flurbiprofen in a quantity of from 1.5 mg/ml to 8.0 mg/ml.

Applicant does agree with the Examiner's conclusion that "Pinza fails to directly teach that the non-steroid anti-inflammatory drug is flurbiprofen." But Pinza '905 also fails to teach that flurbiprofen should be used at the concentration from 1.5% to 8.0% to yield a suitable solution to meet simultaneously all criteria from (a) to (f).

However, the Examiner also states that: "Therefore though Pinza fails to directly state the nature of the dosing pump, a dosing pump must necessarily be present." Upon reviewing Pinza '905, there is mention neither to the term "pump" nor "dosing pump" nor "pressure operating pump". In short, the Examiner lacks a factual basis for the assertion.

Moreover, Pinza '905 also fails to indicate any volume or dose to be used as a medicament. The Examiner will recognize that while the volume or dose is not so stringent for use with a mouthwash (after washing the mouth, the excess of solution is disposed), for a medicinal spray it is essential to dispense an established volume or dose of the active ingredient.

This is clearly stated in several sentences of the description of the instant invention : "In particular the solution is preferably packaged in a multi dose contained equipped with a pressure operating pump, fitted with a dispensing erogator (of variable type and shape) which enables uniform spraying of the solution within the oral cavity."

Attached for the Examiner's reference is Chapter 50 "Aerosols" of the publication "Remington:The Science and Practice in Pharmacy", 20th Ed., 2000. In the "Definitions" section (enclosed page 963) it states that:

"The term aerosol is used to denote various systems ranging from those of a colloidal nature to systems consisting of pressured packages."

"Pumps systems that also dispense the active ingredients(s) in the form of a finely dispersed mist (although of greater particle size) other are classified as aerosols. These pump systems generally are used to dispense medication intranasally."

"Especially important are the metered valves that are essential for medicinal aerosols"

"These valves make it possible to dispense quantities of aerosol ranging from about 25 to 100 µl per actuation."

In conclusion, while the claimed invention discloses a throat, mouth and/or gum sprayable pharmaceutical preparation in the form of aqueous solution containing flurbiprofen in a range from 0.15% to 8.0% with a dispensed volume for each unit dose of from 100 microlitres (0.1 ml) to about 300 microlitres (0.3 ml) (claim 12) where the optimal dispensed volume is 200 microlitres (0.2 ml) (claim 17), Pinza '905 discloses a mouthwash composition containing diclofenac tromethamine salt from 0.1% to 0.2% (NSAID diclofenac content from 0.07% to 0.14%).

The Examiner contends that Caldwell '829 discloses an oral composition comprising a non-steroidal anti-inflammatory, specifically, either diclofenac, flurbiprofen, naproxen or ketoprofen. Further, it is also alleged that Caldwell '829 teaches the use of TRIS (tromethamine) buffer in said composition.

However, Caldwell '829 actually discloses a pharmaceutical composition, having a dispersion containing a mixture of a NSAID with dispersing agents and other auxiliary agents.

A typical embodiment of such a "liquid dispersion" is obtained by admixing the NSAID to an alkali metal such as calcium hydroxide and calcium saccharinate or ammonium salts. Additionally, propylene glycol or polyethylene glycol, ethanol, sorbitol or glycerin may be added to improve the composition of the dispersion. Conventional dispersing agents such as polyvinylpyrrolidone PVP K28-32 or HPC or HPMC may also be added to the liquid dispersion. The liquid dispersion is intended for "oral administration", with the purpose to enable an improved absorption of the NSAID through the gastrointestinal tract to achieve a better systemic effect.

The evidence that the Caldwell '829 composition is intended to yield a systemic effect derives from the sentence that "selected dispersing agents" are "able to disperse non-steroidal anti-inflammatory drugs in the stomach when added to certain oral liquid compositions of the NSAID's prior to ingestion". Caldwell '829 fails to teach that the composition containing the non-steroid anti-inflammatory drug is intended for local effect within the oral cavity in the form of an aqueous solution of flurbiprofen. By contrast, the current invention is intended neither to be ingested nor to exert any systemic effect.

Also considering the Examples highlighted by Examiner, it can be seen that Example 9 contains 1.5% of "Ketoprofen Tris" and Example 10 contains "Naproxen TRIS" in a much higher amount than the range of Flurbiprofen of the present invention which is intended for the application to the oral mucosa (from 0.15% to 0.8%), since higher concentrations may be definitely toxic.

Furthermore, all other Examples disclosed in this document contain even higher concentrations of NSAID, as follows:

Example 2	Sulindac	4.0%
Example 7	Ibuprofen	4.0%
Example 8	Fenoprofen calcium	4.61%

In addition Caldwell '829 teaches that "The oral compositions are usually formulated to deliver about 50-250 mg of drug per teaspoon of a pleasant tasting liquid which will have enhanced activity."

In view of the disclosure in "Remington:The Science and Practice in Pharmacy", 20th Ed., 2000, at page 101 (enclosed copy) which defines that a teaspoon in USA corresponds to the apothecary volume of 2.5 ml, the concentration of NSAID in Caldwell '829 will result in a range from 2.0% to 10.0% respectively, thus confirming that the concentrations of the examples are the expression of this range.

Even using a teaspoon volume of 5.0 ml (this apothecary volume is used outside USA), the NSAID used in Caldwell '829 will still be in the range of from 1.0 to 5.0%.

However, Caldwell '829 further states that "The preferred NSAID's are sulindac, diclofenac, ketoprofen, naproxen and ibuprofen.", thus failing even to mention flurbiprofen.

The restriction of the claims to a solution containing only flurbiprofen differs significantly from the "liquid dispersion" of Caldwell '829, particularly as the concentration now specified in the claims is not suitable to yield a systemic effect. In contrast to that of the present invention which is only suitable for use in the oral cavity.

Therefore and contrary to the Examiner's allegation, it would never have been obvious to one of ordinary skill in the art to utilize the flurbiprofen of Caldwell '829 in the invention of Pinza '905 and in the comments specified to achieve the desired effect on the throat, mouth and/or gum.

The person skilled in the art would never have been motivated to combine Pinza '905 with Caldwell '829 because there is no discussion in the latter of the aim to provide an improved sprayable pharmaceutical preparation exerting its effect on the throat, mouth and/or gum. Even if the skilled person did try and combine the teachings of Pinza '905 with Caldwell '829, since the latter describes a liquid dispersion intended for "oral administration", for subsequent ingestion, and to enable an improved absorption of a NSAID through the gastrointestinal tract to achieve a better systemic effect, the skilled practitioner could never have utilized this document in arriving at an oromucosal solution that does not yield a systemic effect but instead achieves a local effect on the oral cavity.

Pinza '905, Caldwell '829 and Lundberg '281

Similar to the teachings of Caldwell '829 , Lundberg '281is directed towards the preparation of a pharmaceutical formulation in the form of an enteric coated tablet.

Therefore, similar to the reasoning provided above, it would never have been obvious to one of ordinary skill in the art to utilize the flubiprofen at the particular concentration in amended claim 1 and which concentration is not suitable to yield a systemic effect.

One of skill would clearly understand that the solution of the claimed invention is only suitable for use in the oral cavity, thus clearly excluding any overlap or prima facie obviousness with regard to Caldwell '829 (ingestion into the stomach) and Lundberg '281 (proton pump inhibitor) but also Pinza '905 (diclofenac and in a different concentration range).

The Applicant has demonstrated above that claimed flurbiprofen ranges do not "overlap or lie inside ranges disclosed by the prior art" (not its combination) so that examples of criteria cited by Examiner for MPEP 2144.05 are not directly applicable to the instant case since the prior art does not suggest in any way that one skilled in the art look to the range appearing in the prior art.

Examiner's cited reference for MPEP 2144.07 does not apply in respect of the claims as now presented. In Sinclair & Carrol Co. v. Interchemical Corporation it is stated that "Claims to a printing ink comprising a solvent having the vapor pressure characteristics of butyl carbitol so that the ink would not dry at room temperature but would dry quickly upon heating were held invalid over a reference teaching a printing ink made with a different solvent that was nonvolatile at room temperature but highly volatile when heated, in view of an article which taught the desired boiling point and vapor pressure characteristics of a solvent for printing inks and a catalog teaching the boiling point and vapor pressure characteristics of butyl carbitol" .

The applicant has not merely read a list and selected a known compound to meet known requirements, as stated above and the Examiner's objection no longer applies to the new claims presented herewith.

Moreover Applicant respectfully remarks that, as established by Federal Circuit, obviousness cannot be established by combining the teachings of the cited prior art (Caldwell '829, Pinza '905 and even Lundberg '281) to produce the claimed invention, and/or its advantages of higher inventive level over the previous art, absent some teaching, suggestion or incentive supporting the oromucosal solution and the concentration range of flurbiprofen. There must be some intrinsic basis in the prior art or

some extrinsic factor that would prompt one of ordinary skill in the art to combine the teachings of the references; otherwise Examiner's burden of establishing a *prima facie* case of obviousness shall not been established.

Considering the teaching to be drawn from the opposed prior art and the facts and observations here above evidenced, it is not seen in which way the artisan could modify or otherwise optimize in an obvious way the disclosed prior art in order to anticipate the instant invention.

In conclusion a favourable reconsideration of this patent application is respectfully requested and it is hoped that, in the light of the foregoing, the Examiner will now feel able to issue a favourable report.

Respectfully submitted,

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